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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/575,199	05/18/2000	Rodney Alan Jue	SCIOS.010CP1	9828

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EXAMINER
SPECTOR, LORRAINE

ART UNIT	PAPER NUMBER
1647	21

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Please find below and/or attached an Office communication concerning this application or proceeding.

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SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.

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Below is a communication from the EXAMINER in charge of this application

COMMISSIONER OF PATENTS AND TRADEMARKS

ADVISORY ACTION

☒ THE PERIOD FOR RESPONSE:

a) ☐ is extended to run _____ or continues to run _____ from the date of the final rejection

b) ☒ expires three months from the date of the final rejection or as of the mailing date of this Advisory Action, whichever is later. In no event however, will the statutory period for the response expire later than six months from the date of the final rejection.

Any extension of time must be obtained by filing a petition under 37 CFR 1.136(a), the proposed response and the appropriate fee. The date on which the response, the petition , and the fee have been filed is the date of the response and also the date for the purposes of determining the period of extension and the corresponding amount of the fee. Any extension fee pursuant to 37 CFR 1.17 will be calculated from the date of the originally set shortened statutory period for response or as set forth in b) above.

☐ Appellant's Brief is due in accordance with 37 CFR 1.192(a).

☐ Applicant's response to the final rejection, filed _____ has been considered with the following effect, but it is not deemed to place the application in condition for allowance:

1. ☒ The proposed amendments to the claim and /or specification will not be entered and the final rejection stands because:

a. ☐ There is no convincing showing under 37 CFR 1.116(b) why the proposed amendment is necessary and was not earlier presented.

b. ☐ They raise new issues that would require further consideration and/or search. (See Note).

c. ☐ They raise the issue of new matter. (See Note).

d. ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal.

e. ☐ They present additional claims without cancelling a corresponding number of finally rejected claims.

NOTE: _____

2. ☐ Newly proposed or amended claims _____ would be allowed if submitted in a separately filed amendment cancelling the non-allowable claims.

3. ☒ Upon the filing an appeal, the proposed amendment ☒ will be entered ☐ will not be entered and the status of the claims will be as follows:

Claims allowed: None

Claims objected to: _____

Claims rejected: 1-3, 5-11, 13-21, 25

However;

☒ Applicant's response has overcome the following rejection(s): 112 2nd

4. ☒ The affidavit, exhibit or request for reconsideration has been considered but does not overcome the rejection because Art rejection maintained for reasons of record.

5. ☐ The affidavit or exhibit will not be considered because applicant has not shown good and sufficent reasons why it was not earlier presented.

☐ The proposed drawing correction ☐ has ☐ has not been approved by the examiner.

☐ Other

Lorraine Spector

LORRAINE SPECTOR
PRIMARY EXAMINER

PTOL-303 (REV. 5-89)

Part III: Detailed Office Action

Restriction Requirement:

Applicant's election of Invention I, claims 1-34, with an election of species wherein VEGF comprises residues 4-116 in Paper No. 9, filed 2/25/02, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Formal Matters:

With the exception of the cited US Patents and the Keck reference (item 62), documents listed on the Information Disclosure Statement filed 1/9/01, paper number 4, were not available to the Examiner at the time of examination. Applicants may, in response to this and no later Office Action, submit the missing references. Such submissions will be considered to have been part of the Information Disclosure Statement filed 1/9/01, and the PTO-1449 will be updated accordingly. No fee for the submission of such references is required, nor should applicants file an additional form PTO-1449 with the missing references.

Claims 28-34 are objected to for encompassing multiple, patentably distinct inventions. Applicants are required to amend the claims to recite only the elected invention, wherein both Cys_{116} residues are bound to extraneous Cys residues.

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The disclosure is objected to because of the following informalities: The specification should be carefully reviewed for typographical errors. For example, the word "The" is misspelled at page 19, line 9.

Appropriate correction is required.

Objections and Rejections under 35 U.S.C. §112:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 14 and 28 are indefinite because, using claim 1 as an example, the claims recite that each monomer is "retaining a cysteine at or corresponding to position 116 of SEQ ID NO: 1", "wherein Cys-116 of each monomer is disulfide-bonded..."; if the Cys in question is only at a position *corresponding* to position 116 of SEQ ID NO: 1, then there is no requirement for a Cys *at* position 116 of the monomer. Amendment to recite "wherein said Cys of each monomer is..." or the equivalent would be remedial.

Claims 4 and 17 are further indefinite for failing to adequately point out that which applicant sees as the invention. The specification specifically relates to the condition of Cys-116, whereas claims 4 and 17 do not specify which of the 8 or more possible cysteine residues is bonded to a glutathione moiety. Further, if the claims were amended to indicate that it is the cysteine corresponding to position 116 of SEQ ID NO: 1 that is in question, they would be duplicative of claims 3 and 16, respectively.

The remaining claims are rejected for depending from an indefinite claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (a) dimers which comprise monomers of VEGF-121 or active fragments

or derivative ≥90% identical thereto, (b)dimers comprising monomers terminating at residues 120 or 121 of SEQ ID NO: 1, and (c) dimers in the form of heterogeneous mixtures comprising molecules wherein both monomers have Cys-116 bound to an extraneous Cys, does not reasonably provide enablement for (a) dimers which comprise monomers of longer (165 amino acids or longer) forms of VEGF, (b)dimers comprising monomers terminating at residues 116-119 of SEQ ID NO: 1, or (c) dimers in the form of homogeneous, 75% pure, 85% pure, or 95% pure preparations (as recited in claims 32-34) of molecules wherein both monomers have Cys-116 bound to an extraneous Cys, such dimers "essentially free" of other forms as recited in claims 26-27, or such dimers as the "main component" of a composition, as recited in claim 31. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Each of the above issues will be addressed in turn:

(a) Dimers which comprise monomers of longer (165 amino acids or longer) forms of VEGF:

The five naturally occurring forms of VEGF are due to alternative splicing of the mRNA which encodes the protein. As evidenced by Keck et al. (Archives of Biochemistry and Biophysics, 344:1:103-113, August 1, 1997, cited by applicants), the 165, 189 and 206- amino acid forms of the protein diverge from the 121 amino acid form of the protein at residue 116. Accordingly, there *is* no residue in the longer forms which corresponds to Cys 116 of SEQ ID NO: 1, as there *is* not Cys-116 in the longer forms. Further, applicants have disclosed in the specification that the 121 amino acid form forms bonds with extraneous cysteines and is more stable at room temperature when the two cysteines at position 116 are bonded to extraneous cysteines, however such is not enabling of

any equivalent showing for the longer forms. As discussed above, the longer forms of VEGF do not comprise a cysteine residue at the position corresponding to residue 116 of SEQ ID NO: 1 (the 121-amino acid form of VEGF). Accordingly, it is not clear how one of ordinary skill in the art would be able to make the claimed dimers as they are drawn to the ≥165-residue forms of the protein. Further, even *if* such a form could be made, it is not predictable that it would have the disclosed properties of the -121 amino acid form of being more stable in solution at room temperature. The nature of the invention is the characterization of the Cys-116 residues as being bound to extraneous (free or part of a small peptide) cysteines. The prior art is silent with respect to this feature. Further, the prior art teaches that the various forms of VEGF have different properties, notably that VEGF 121 does not bind to heparin whereas the longer forms do, that VEGF-121 and 165 are soluble, whereas VEGF 189 and 206 are found to be associated with the extracellular matrix (see Keck et al., cited *supra*). Given that VEGF 121 lacks the heparin binding domain that is at the C-terminus of the longer forms, the skilled artisan would not consider it predictable that binding Cys residues at position 116 of the longer forms would have an equivalent affect to the same as applied to the short form. Although the skill in the art is high, this is a feature of the protein that was previously unappreciated, including the result that such renders the protein more stable. There are no working examples other than VEGF-121. The claims are broad, with no limitations to any particular form of VEGF, nor any particular sequence thereof, given the recitation of 90% identity. There is no guidance in the specification as to how to make forms of the longer VEGF molecules which are bound at position 116 to extraneous cysteine residues. Considering all these factors, the Examiner concludes that it would require undue experimentation to make and use the invention as it is drawn to the longer forms of VEGF.

(b) Dimers comprising monomers terminating at residues 116-119 of SEQ ID NO: 1:

The specification discloses production of VEGF-121, and demonstrates that the molecules recovered were heterogeneous, terminating at either residue 120 or 121, see paragraph bridging pages 29-30. There is no guidance nor working examples as to how to produce shorter forms, nor what

the properties of such would be. Although the art in recombinant production of proteins is high, such that one of ordinary skill in the art would easily be able to manufacture DNA encoding such shorter forms, the behavior of such in recombinant expression systems is unpredictable, as evidenced by the spontaneous production of a 120 amino acid form when only DNA encoding a 121 amino acid form was present. Such production of a shorter form may be due to degradation of the protein by the host cell, or alternatively to incomplete translation of the mRNA encoding the protein. There is no characterization of the cause of the shorter form in the specification as originally filed. It is unpredictable that one of skill in the art would be able to make forms of VEGF terminating at residues 116, 117, 118 or 119 without undue experimentation because (I) it is not predictable whether or not such forms would also be spontaneously degraded as was the case for VEGF 121 such that a particular form might not be obtainable using methods taught in the specification as originally filed, (ii) it is not predictable that such shorter forms would form disulfide bonds between Cys-116 and an extraneous cysteine as was observed for VEGF 121, (iii) it is not predictable that, if such bonding occurred, that it would be stable, and (iv) it is not predictable what the effect of such bonding would be on the molecule as a whole. Given the lack of guidance, the lack of pertinent teachings in the art, the lack of working examples of such shorter forms, and the unpredictability of protein stability and disulfide bonds and their effect, the invention is not enabled for forms of VEGF which terminate prior to residue 120 of SEQ ID NO: 1.

(c) Dimers in the form of homogeneous, 75% pure, 85% pure, or 95% pure preparations (as recited in claims 32-34) of molecules wherein both monomers have Cys-116 bound to an extraneous Cys, such dimers "essentially free" of other forms as recited in claims 26-27, or such dimers as the "main component" of a composition, as recited in claim 31:

The specification discloses at page 3 that extraneous cysteine residues at position 116 enhance stability of VEGF-121. At line 15 of that page, the specification discloses that the extraneous cysteine residues may be part of a peptide comprising 2-5, preferably 2-3 amino acids, such as glutathione. At page 19, the specification teaches that "By adjusting the amounts and mutual

ration of cysteine and cystine, one can produce the desired mix of VEGF dimers", and gives preferred ratios for such. At page 21, the specification states that "By modifying the conditions during production stages, e.g. by including cysteine, cystine and/or glutathione in the medium, the form of VEGF121 dimer can be modulated such that the majority of the product is in a form containing a mixed disulfide at Cys-116." However, the three working examples fail to demonstrate any intentional manipulation of the type of product produce: Example 1, beginning at page 26, demonstrates the production of VEGF121 in CHO cells. There is no extra cysteine, cystine or glutathione added to the medium, nor any active step included that would alter the type of protein produced with respect to Cys-116. Although the specification states at page 29 line 12 that in 'some cases two extra cysteine molecules had become bonded to the VEGF dimer", there is no disclosure of how much of the product was comprised by that species, nor how to affect the proportions of the product. Example 2, beginning at page 30, discloses expression of VEGF-121 in E. coli. Once again, there are no active steps taken to influence the cysteine composition of the product. At page 32, last paragraph, it is stated that the time allowed for refolding affects the proportion of extra cysteines, with longer times favoring more extraneous cysteines. However, no precise conditions are given, nor any guidance as to such conditions, or the amount of the claimed product (with Cysteines at residue 116 of each monomer making up the dimer) obtained disclosed, nor is there guidance as to the maximum amount that could reasonably be obtained. Example 3, in which VEGF-121 was produced in *Pichia pastoris*, yielded a product in which the Cys-116 residues were disulfide bonded to each other.

As was found above, the nature of the invention is the characterization of the Cys-116 residues as being bound to extraneous (free or part of a small peptide) cysteines. The prior art is silent with respect to this feature and thus silent with respect to how to optimize this feature. The specification provides only vague guidance and no working examples in which the proportion of desired product was manipulated, such that the specification is considered to provide only an invitation to experiment to determine how to produce a protein comprised of 75, 85 or 95% of the desired dimer, in which both monomers have extraneous Cys residues bound at position 116, nor

such dimers "essentially free" of molecules which are bound together at residue 116 or unbound at residue 116. Accordingly, the specification is not enabling of the claimed ranges.

Rejections Over Prior Art:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-25 and 28-30 are rejected under 35 U.S.C. 102(b) as being anticipated by Tischer et al., U.S. Patent Number 5,194,596, cited by applicants.

Tischer et al. disclose recombinant production of VEGF-121; see claims. At columns 34-35 they specifically disclose recombinant production in mammalian cells or bacterial expression systems, and outline at the top of col. 35 a method for refolding protein produced in bacterial cells in a solution comprising glutathione. Pharmaceutical compositions are disclosed at columns 10-12. Although Tischer et al. are silent with respect to whether or not the cysteine residues at position 116 were bound to extraneous cysteine residues, given the examples in the instant specification, in which such occurred with no overt action on the part of the inventors, and in the absence of any added cysteine or glutathione such is considered to have been inherent to the proteins produced by the methods of Tischer et al. Further, since Tischer et al. disclose using glutathione to refold the protein, it would be expected that proteins having glutathione bound to Cys-116 would also be obtained. The Examiner notes that the case law supports the finding of inherency; in *In re:Swinehart and Sfiligoj* (169 USPQ 226), it was found that "Mere recitation of newly discovered function or property, inherently possessed by things in prior art, does not cause claim drawn to those things to distinguish over prior art." In this case, one following the teachings of Tischer et al. would necessarily obtain products consistent with the claims.

Advisory Information:

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector, whose telephone number is (703) 308-1793. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 5:30 P.M.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary L. Kunz, at (703)308-4623.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist at telephone number (703) 308-0196.

Certain papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to (703) 872-9306 (before final rejection) or (703)872-9307 (after final). Faxed draft or informal communications with the examiner should be directed to (703) 746-5228.

Lorraine Spector, Ph.D.
Primary Examiner

LMS
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6/28/02